Management of Obscure Gastrointestinal Bleeding

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INTRODUCTION

Obscure gastrointestinal bleeding (GIB) is defined as bleeding without an identifiable source in the gastrointestinal tract (1). The American College of Gastroenterology denotes GIB as obscure after unrevealing upper and lower endoscopic examinations, small bowel video capsule endoscopy (VCE)/enteroscopy, and radiographic testing (2). The presentation of obscure GIB can be either overt (hematemesis or melena) or occult (nonspecific symptoms such as fatigue). The most common etiologies for obscure GIB are Dieulafoy's lesions, angioectasias, and neoplasm. Obscure GIB often leads to recurrent bleeding episodes and hospital admissions (2). In this review, we discuss the current and emerging management options mainly for patients with hemodynamically stable obscure GIB, in which standard evaluation with at least bidirectional endoscopy and possibly push enteroscopy, VCE, computed tomography enterography (CTE), double-balloon enteroscopy were already exhausted for a source (Figures 1 and 2).

ENDOSCOPIC EVALUATION

Second-look endoscopy

In patients with unrevealing initial upper and lower endoscopic evaluation, the typical approach is to repeat the endoscopic examinations (based on presentation) in hopes of finding lesions that have been previously undetected (3–6). Studies have reported success rates of up to 25% for the second-look esophagogastroduodenoscopy (EGD)/colonoscopy in identifying the GIB etiology (4). Push enteroscopy can be an alternative to second-look EGD due to cost-effectiveness in suspected upper GIB and ability to evaluate duodenum and proximal jejunum better than VCE which is limited due to rapid transit through this area (7).

Video capsule endoscopy

VCE is often helpful when used within the first 48 hours of detection of an obscure GIB; however, the yield goes down further if delayed beyond 2 weeks (3). VCE can successfully identify the etiology of bleeding in 63%–67% of patients with obscure GIB, especially when the bleeding is clinically overt (6). In a recently published, large retrospective analysis of obscure GIB manifesting in patients with left ventricular assist devices (LVADs), VCE demonstrated excellent diagnostic yield (68.9%) as a first-line diagnostic tool (7). A positive VCE finding is usually subsequently evaluated through enteroscopy to reach and treat the culprit lesion. If an initial VCE is negative, repeat VCE can be considered; however, the diagnostic yield of second-look capsule examination reported in studies has been variable and is in the range of 35%–49% (4).

Enteroscopy

In addition to aiding in the diagnosis, enteroscopy can help treat the bleeding lesion. device-assisted enteroscopy (DAE), such as single-balloon, double-balloon, and spiral enteroscopy, can be performed as first-line alternative to VCE, as total enteroscopy has higher effectiveness for both diagnostic and therapeutic yield compared with VCE (3,4). VCE-guided DAE can be a viable option in resource limited settings where DAE is not readily available or to reduce procedural risks associated with prolonged procedures in ill patients. DAE also has higher yield when performed after positive VCE which supports VCE-guided DAE. Positioning of DAE could be first line (total enteroscopy), after VCE for guided VCE-DAE (highest yield) or after VCE is negative but high clinical suspicion remains for small bowel bleeding; all 3 options can be correct but depend on clinical scenario and availability of resources. Intraoperative enteroscopy, performed during laparotomy using an enteroscope inserted peroral or through enterotomy, is associated with significant morbidity and is reserved as one of the last management options in patients with repeated bleeding episodes requiring multiple transfusions, hospitalizations, and other negative testing (4).

RADIOGRAPHIC EVALUATION

Enterography

CTE and magnetic resonance enterography (MRE) are performed after ingesting enteric contrast material to distend the small bowel and increase mucosal resolution, in addition to intravenous contrast (6,8). Studies have shown variable identification rates of GIB etiology with CTE and MRE, depending on the amount of bleeding. CTE is recommended over MRE due to overall lack of evidence for MRE in GIB, unless radiation is to be avoided in young patients. CTE is also more readily available, faster in most settings, and does not have contraindications such as LVAD hardware. CTE and MRE both use nonbarium neutral contrast ("water-like"). This is an important concept as regular oral contrast is radiopaque and can obscure sources of GIB such

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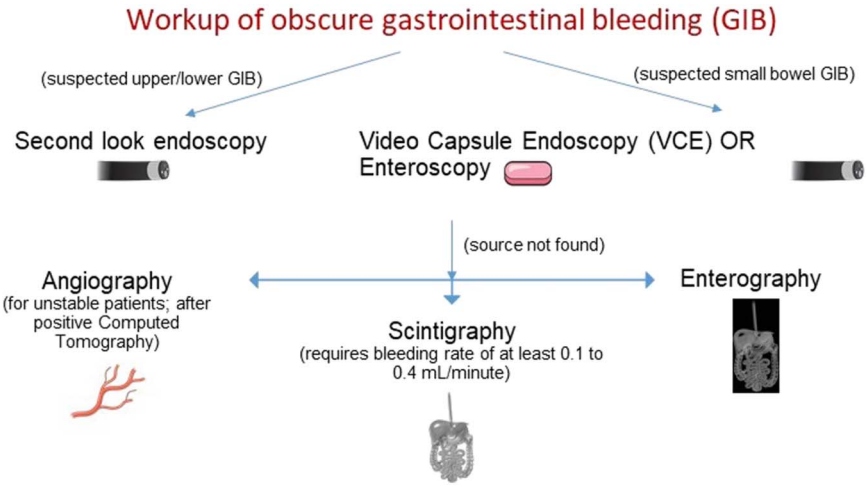
Workup of obscure gastrointestinal bleeding (GIB)
(suspected upper/lower GIB)
(suspected small bowel GIB)
Second look endoscopy
Video Capsule Endoscopy (VCE) OR Enteroscopy
(source not found)
Angiography
(for unstable patients; after positive Computed Tomography)
Scintigraphy
(requires bleeding rate of at least 0.1 to 0.4 mL/minute)
Enterography

Figure 1. Workup of obscure gastrointestinal bleeding. GIB, obscure gastrointestinal bleeding.

as masses, ulcers, or even blushes of contrast from active bleeding. Therefore, barium studies are not recommended. CTE (or MRE) can detect masses with better sensitivity than VCE, so should be considered as complementary study for small bowel evaluation.

Scintigraphy

Radioisotope bleeding scans are sensitive for identifying GIB sources, such as technetium 99m-labeled red blood cell scintigraphy (75% sensitivity) and Meckel scintigraphy (62%–87.5% sensitivity for ectopic gastric tissue) (4). The latter should be pursued in young patients with obscure and overt bleeding. These scans, however, are time-consuming, require a bleeding rate of at least 0.1–0.4 mL/min, and are often not able to accurately localize the specific site of bleeding. The ACR recommends combining radionuclide scans with Single Photon Emission Computed Tomography scan to enhance the localization capability (6).

Angiography

Computed tomograph angiography (CTA) is a multiphased study with at least 3 phases including noncontrast, late arterial phase, and late venous or portal venous phase to allow localization of bleeding (3–6). Earlier, bleeding rate of 0.5–1 mL/min was needed to be detected by CTA, but newer modalities can detect rate as slow as 0.1 mL/min. The limitation of CTA is use of intravenous contrast which is a major barrier in many patients with small bowel bleeding due to comorbidities such as chronic kidney disease. Direct angiography is rarely performed before CTA in practice and is typically reserved for positive CTA when patients are unable to undergo endoscopy. Provocative angiography is still an option for evaluation of obscure GIB, although it is falling out of favor.

MANAGEMENT

Endoscopic hemostasis

A positive finding detected during patient evaluation is generally followed by the appropriate endoscopic technique to both reach the lesion in question and achieve hemostasis, especially for angiodysplasias. The commonly used modalities are bipolar cautery or Argon Plasma Coagulation with or without saline lift or epinephrine injection to prevent deep tissue injury or application of hemostatic clips. With the increasing availability of variously sized and shaped hemostatic clips, these devices have become a preferred approach to achieve hemostasis at many centers. In a retrospective study, patients with angiodysplasias had a lower rate of rebleeding with hemoclips combination therapy as compared with Argon Plasma Coagulation alone after resuming antithrombotic therapy (9). Case reports describe successful use of band ligation, radiofrequency ablation, and hemostatic sprays and powders (5). It is worth mentioning that around one-third patients with angiodysplasias can have rebleeding after endoscopic therapy (10).

Somatostatin analogs

Octreotide, a somatostatin analog, has antivascular endothelial growth factor properties and can cause vasoconstriction limiting the amount of bleeding from angiodysplasias (11). A prior patient-level meta-analysis of 11 studies showed that 83% of patients with angiodysplasias treated with somatostatin analogs had at least 50% reduction in the number of red blood cell transfusions (11,12). Patients on octreotide had better treatment response than lanreotide. Around 5% of patients discontinued the therapy because of adverse events, which occurred in around 18% patients. The newly published "Efficacy of Octreotide on Blood and Iron Requirements in Patients With Anemia Due to Angiodysplasias" (OCEAN) trial randomized patients to standard of care with or without 40 mg intramuscular octreotide every 28 days for 52 weeks (11). As compared with standard of care alone, patients who received adjunctive octreotide had a significantly decreased mean number of transfusion units (11 vs 21.2, $P = 0.012$) and endoscopic procedures (0.3 vs 1.2). Adverse events were comparable in the octreotide (71%) and standard of care (68%) groups. The number-needed-to-treat was only 2 for at least 50% reduction in transfusion requirements. The OCEAN trial showed promising results with potential to change clinical guidelines for angiodysplasia-related GIB. Octreotide can be administered subcutaneously or intramuscularly (long-acting form, once per month) outpatient. It is important to keep in mind that while the OCEAN trial is promising, there has been other data that have not shown similar robust benefit (12). In addition, GIB is not an approved indication by US Food and Drug Administration for depot/standard octreotide; hence, it is often a very cost-prohibitive option for patients.

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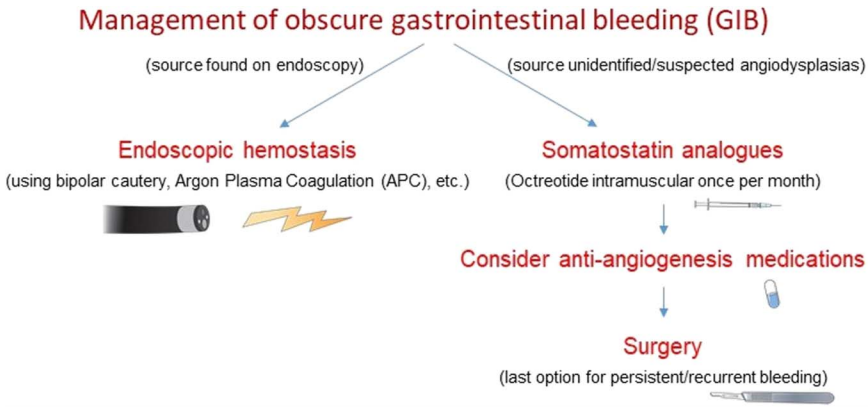

Figure 2. Management of obscure gastrointestinal bleeding. GIB, obscure gastrointestinal bleeding.

Antiangiogenesis medications

Patients with an established history of angiodysplasia and recurrent GIB can be challenging to manage, especially when the bleeding source remains obscure despite multiple investigations. Antiangiogenesis medications can have a therapeutic role in such patients (11). In a randomized controlled trial of patients with recurrent or refractory GIB due to vascular malformations, 71.4% patients treated with thalidomide had a ≥50% decrease in bleeding episodes in the first year of follow-up, compared with 3.7% patients in a control group treated with iron alone (13). Thalidomide was also found to be superior in producing a higher rate of cessation of bleeding and decreased need for blood transfusions and hospitalizations (13).

A recent randomized controlled trial of thalidomide versus placebo by Chen et al (14) among patients with small intestinal angiodysplasia-related recurrent GIB showed reduction of at least 50% bleeding episodes in 68.6%, 51.0%, and 16.0% patients treated with 100 mg/d thalidomide, 50 mg/d thalidomide, and placebo, respectively. The sample size of the study (150 patients) and ethnic restriction (Chinese population) limit the generalizability of the results but given the significant morbidity and mortality associated with recurrent GIB, benefits with thalidomide may outweigh the potential side effects in carefully selected patients (14). Owing to high risks associated with thalidomide, it requires special prescriber license, close follow-up, careful patient selection, and is best performed in collaboration with hematologists.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has shown some efficacy in patients with angiodysplasias and arteriovenous malformations associated with LVADs (12,15). Only a few case reports/series have studied bevacizumab for GIB without any control groups (12). Overall, at this time, the role of bevacizumab for obscure GIB remains unclear. Similarly, danazol, an androgen-like steroid which decreases endothelial permeability, has also shown some benefit in patients with LVAD; however, the overall evidence is low (15). Furthermore, because anticoagulant/antithrombotic agents are often used in patients with LVAD to prevent thrombosis, optimal management of these medications is important in patients with recurrent GIB episodes (15).

CONCLUSION

Obscure GIB accounts for approximately 5% of all GIB cases. Endoscopic modalities, including second-look EGD/colonoscopy, VCE and enteroscopy, remain the cornerstone of initial diagnosis and therapy in patients with obscure GIB. In cases with persistent/recurrent GIB, other management options include an interventional radiographic approach, medications such as octreotide and thalidomide, and rarely, surgery.

CONFLICTS OF INTEREST

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